The goal of antiretroviral therapy (ART) is maximal virologic suppression to levels of HIV RNA that are undetectable with ultrasensitive viral load assays. This goal is readily achievable in patients who are adherent to potent regimens, as indicated by the high rates of success observed in clinical trials and observational cohort studies. Nevertheless, patients sometimes have detectable viral loads even under the best of circumstances. In fact, the situation is common enough to require new terminology, resulting in the introduction of the delightful term “blip” into our medical vocabulary. A blip is generally defined as a single, low-level but detectable plasma viral load measurement (e.g., 50–1000 copies/mL) that is immediately preceded and followed by a viral load below the limit of detection.

The causes and clinical implications of blips have been debated, and the data are far from consistent. Potential explanations for blips can be divided into 2 broad categories on the basis of whether they are viewed as episodes of true viremia due to viral replication or as artifactual measurements. Support for the latter viewpoint includes evidence that blips may represent random biologic or laboratory variation around a mean viral load that is below the limits of detection. In a study by Nettles and colleagues [1], intensive sampling of patients who received stable, suppressive ART found that blips were common, of low magnitude and limited duration, not associated with development of resistance mutations, and not concordant across laboratories. It has also been suggested that many blips are a result of the release of virus from a latent reservoir [2].

The development of more sensitive viral load assays, specifically version 1.5 of the Amplicor ultrasensitive reverse transcriptase–polymerase chain reaction assay (Roche Diagnostics), also led to a marked increase in the proportion of patients with viral loads that were detectable at low levels. This problem received considerable attention because of the unprecedented inconsistency between virologic efficacy determined with the standard viral load assay (which has a limit of detection of <400 copies/mL) and that determined with the ultrasensitive assay (which has a limit of detection of <50 copies/mL) in the BMS 034 trial comparing efavirenz with atazanavir [3]. The cause of this inconsistency was ultimately determined to be a combination of greater sensitivity of the assay and improper processing of specimens by laboratories, which spun, froze, and stored plasma preparation tubes, allowing the continued release of virus into plasma by HIV-infected lymphocytes and thus creating artifactual increases in measured viral loads [4]. If our clinic at Johns Hopkins is at all representative, false-positive viral load measurements caused by improper specimen processing resulted in unnecessary clinic visits, viral load and resistance testing, and treatment modification or intensification, not to mention a great deal of anxiety on the part of patients and clinicians. Most laboratories have now corrected this error in processing, using either EDTA or plasma preparation tubes that are spun and separated immediately before freezing and storage. However, in our experience, there are still some commercial laboratories that continue to report unreliable viral load results. Whether this is caused by incorrect processing of samples or some other problem is unclear.

In contrast, some investigators have argued that blips cannot all be explained by random laboratory variation or error and that some may represent true viremia [5, 6]. This view would be bolstered by the demonstration of a clear association between nonadherence to antiretroviral therapy and blips, although the evidence for such an association has been weak to date. In the Nettles study [1], there was no association between blips and antiretroviral...
It was reassuring that in this study, as in most other recent studies, blips were not associated with an increased risk of virologic failure or the development of resistance. This has not always been the case, as some earlier studies demonstrated the emergence of new resistance mutations [8–10] or virologic failure [11, 12] in patients experiencing blips. The lack of an apparent association between blips, the development of resistance, and virologic failure in the more recent studies, even assuming that blips do represent viral replication, could be explained by the use of more potent antiretroviral regimens with higher genetic barriers (ritonavir-boosted protease inhibitors) or pharmacokinetic barriers (nonnucleoside reverse transcriptase inhibitors) to resistance.

How can we make sense out of the conflicting data? Are blips caused by viral replication, the harmless release of virus from resting reservoirs, nonadherence, or just a laboratory technician who has not read the manual? Are blips benign, or can they lead to the development of resistance and virologic failure? The answer is probably “all of the above.” There is now strong evidence that blips can occur randomly without viral replication, and processing errors clearly contributed to a “blip epidemic” (“blipidemic”) that occurred several years ago. On the other hand, we know that the emergence of resistance and the onset of virologic failure has to begin somewhere. Just as we know that persistent low-level viremia is a precursor to overt treatment failure [13–16], it is also plausible that blips could be precursors to persistent low-level viremia. A patient who is nonadherent to therapy and ultimately destined to develop a resistant infection or experience treatment failure might begin that process with a blip.

For clinicians, the problem with blip studies is that they all have the benefit of hindsight. In clinical practice, blips can only be defined after the fact. Until the viral load measurement is repeated, there is no way to know whether a detectable viral load is a blip or the onset of virologic failure—a meaningless laboratory abnormality or evidence of nonadherence. The study by Podsadecki and colleagues [7] points out that in addition to repeating the test, we should also use blips as an opportunity to talk to patients about adherence to therapy.

References

11. Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viremia in patients with initial vi-